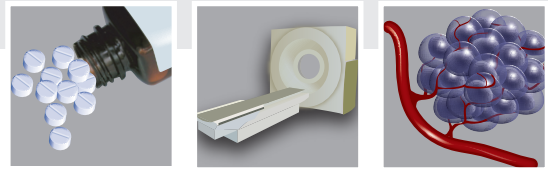


Bulletin Board

Anticancer activity of a bacterial cell wall complex may prove effective in treating bladder cancer

Many studies have shown that cell wall skeletons isolated from a range of bacteria possess anticancer activity. A cell wall extract from *Mycobacterium phlei* has exhibited anticancer activity against a range of cancer cells. This anticancer/antineoplastic activity has been attributed to the presence of DNA. Mycobacterial cell wall–DNA complex (MCC) is a cell wall composition that has mycobacterial DNA in the form of short oligonucleotides complexed onto the cell wall surface. Researchers at Bioniche (Ontario, Canada) have observed that MCC has demonstrated effectiveness as an immunomodulator and anti-tumor agent. It is believed that MCC has a dual mode of action, in which it induces apoptosis in cancer cells as well as stimulating cytokine release.

> "(The) mycobacterial cell wall–DNA complex has shown antineoplastic (anticancer) activity in patients with bladder cancer with less toxicity than that associated with bacillus Calmette–Guerin administration."

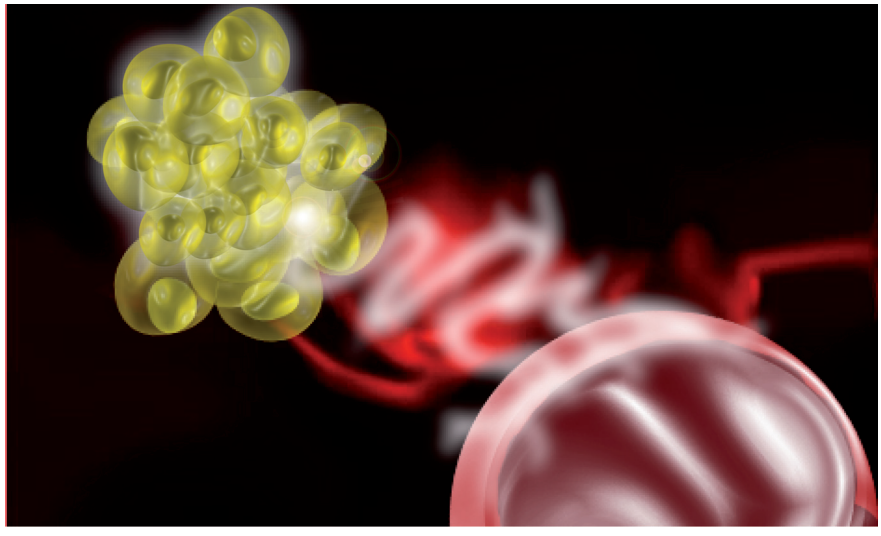
A recent study published in the *Journal of Urology* has shown that MCC displays antineoplastic activity in patients with bladder cancer. The toxicity observed is less than that associated with Bacillus Calmette–Guerin (BCG) administration, suggesting that MCC may be a promising treatment in the battle against bladder cancer.

In this Phase II study, researchers assessed the clinical efficacy and safety of MCC in bladder cancer patients in whom previous therapy with BCG had failed or who were treatment-naive. A total of 55 patients participated in the study, of which 74.6% were male. Among these, 25 individuals received 4 mg and 30 patients received 8 mg of MCC. Patients received 6 weekly instillations of MCC followed by 3 weekly instillations at weeks 12 and 24. Efficacy and safety were evaluated throughout the treatment phase and at months 12 and 18. In the intent-to-treat population, the complete response rate at weeks 12 and 26 in the 4-mg group was 27.3%, while the 8-mg group had a complete response rate of 46.4% at both time points. Complete response was defined as no evidence of the disease as determined by cytoscopy, biopsy and cytology. MCC was well tolerated at both doses, and 90% of all adverse events were mild-to-moderate in severity.

Dr Alvaro Morales, Director of the Center for Advanced Urological Research and Professor in the Department of Urology, Queen's University, Canada, commented on the results: "We concluded that mycobacterial cell wall–DNA complex has shown antineoplastic (anticancer) activity in patients with bladder cancer with less toxicity than that associated with bacillus Calmette–Guerin administration". Morales continued: "Safety concerns exist with BCG because it is a live mycobacterium and its use is associated with a number of local and systemic side effects, as well as the potential for proliferation and systemic dissemination."

Such promising results have supported the initiation of a Phase III clinical trial, evaluating MCC in patients with non-muscle-invasive bladder cancer whose cancer is specifically refractory (unresponsive) to BCG. A total of 31 urology centers in North America are participating in this trial and recruitment is expected to be complete by the end of March 2009.

Source: Morales A, Phadke K, Steinhoff G: Intravesical mycobacterial cell-wall–DNA complex in the treatment of carcinoma *in situ* of the bladder after standard intravesical therapy has failed. *J. Urol.* 181(3), 1040–1045 (2009).



in the news...

Study identifies promotory role of proepithelin in prostate cancer

Researchers from Thomas Jefferson University, PA, USA, have identified evidence of a role for proepithelin in the growth and migration of prostate cancer cells. Proepithelin is a growth factor that promotes cell-cycle progression, and has previously been shown to have a role in other malignancies, such as bladder cancer and breast cancer. The study by Monami *et al*. is the first to show its involvement in the growth of prostate cancer cells.

The study led by Andrea Morrione included analysis of prostate cancer microarray studies and found a significantly higher expression of proepithelin mRNA in prostate cancers compared with nonneoplastic controls. The overexpression of proepithelin in prostate cancer cells has two possible implications for future study. Morrione explains, "proepithelin could be a therapeutic target since it is overexpressed in prostate cancers" and "proepithelin could serve as a biomarker and be a diagnostic tool".

The results of the study also suggest that proepithelin may have a role in prostate cancer metastasis. Monami and colleagues found that the growth factor promoted the migration of androgen-dependent and -independent human prostate cancer cells, which is necessary for tumor metastasis. Proepithelin overexpression therefore may have potential as a biomarker for metastasis, which is important as there are currently no reliable markers for the identification of patients who are likely to progress to metastatic disease. The results of the study will be presented at the 2009 ASCO Genitourinary Cancers Symposium.

Source: Monami G, Emiliozzi V, Bitto A *et al.*: Proepithelin regulates prostate cancer cell biology by promoting cell growth, migration, and anchorage-independent growth. *Am. J. Pathol.* 174, 1037–1047 (2009).

Study suggests green tea blocks action of anticancer drug bortezomib

Unexpected results from research into the interaction between green tea and cancer chemotherapy suggest that components of green tea are in fact detrimental to the anticancer effects of a drug used to treat multiple myeloma and mantle cell lymphoma. The study led by Axel Schonthal from University of California, CA, USA, demonstrates that green tea, a popular complementary therapy for cancer patients undergoing chemotherapy, actually has the potential to block the action of bortezomib (marketed as Velcade®).

Researchers aimed to investigate whether the combination of green tea and bortezomib would yield increased antitumor efficacy in multiple myeloma and glioblastoma cell lines. Contrary to expectations, this study found that components of green tea extract (GTE), expecially epigallocatechin gallate (EGCG), prevented tumor cell death induced by bortezomib *in vitro* and *in vivo*. This pronounced antagonistic effect of EGCG was not found in several nonboronic proteasome inhibitors. These findings were not expected by the research team, as Schonthal makes clear; "our hypothesis was that GTE or EGCG would enhance the anti-tumor effects of Velcade, and that a combination of GTE or EGCG with Velcade would turn out to be a superior cancer treatment as compared to treatment with Velcade alone". The study by Golden *et al.* then investigated the mechanism behind the interaction between EGCG and bortezomib, and proposed that EGCG directly blocked the anticancer drug's proteasome inhibitory function by forming chemical bonds with it, and thus preventing its induction of tumor cell death.

"The most immediate conclusion from our study is the strong advice that patients undergoing cancer therapy with Velcade must avoid green tea, and in particular all of its concentrated products that are freely available from health food stores," Schonthal warns. The findings of this study imply that green tea polyphenols have the potential to negate the therapeutic effects of bortezomib, and thus warrant further study to determine whether GTE may be contraindicted during cancer therapy with bortezomib.

Source: Golden EB, Lam PY, Kardosh A *et al.*: Green tea polyphenols block the anticancer effects of bortezomib and other boronic acid-based proteasome inhibitors. *Blood* DOI: 10.1182/blood-2008-07-171389 (2009) (Epub ahead of print).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of oncology. If you have newsworthy information, please contact:

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Safer nanoparticles developed for tumor detection and drug delivery

Nanoparticles have enormous potential for efficient cancer diagnosis and drug delivery, but the safety of this technology is often a major concern. Significant quantities of nanomaterials are cleared by the mononuclear phagocytic system before finding their targets, increasing the likelihood of unintended toxicity. However, a team at the University of California, CA, USA, has developed the first luminescent nanoparticle purposely designed to minimize toxic side effects.

> "The new design meets a growing need for nontoxic alternatives that have a chance to make it into the clinic to treat human patients."

The study, led by Micheal Sailor, and published in *Nature Materials* details a novel design of nanoparticle that breaks down *in vivo* after it has delivered its drug. The new technology is based on flakes of luminescent silicon that self destruct into nontoxic, systematically eliminated, particles. The inherent luminescent property of the nanoparticles enables them to be monitored *in vivo*, and avoids the use of toxic organic chemicals or quantum dots for tracking, which can potentially leave traces of heavy metals behind.

When the nanoparticles were tested in mice, the researchers noted that tumors glowed for several hours, then dimmed as particles broke down, and the nanoparticles were undetectable after 4 weeks. The researchers report that these luminescent particles can reveal tumors too small for detection by other methods and could be used to check for the complete removal of a tumor after surgery. Park *et al.* report that the silicon nanoparticles can help deliver drugs safely, and the cancer drug doxorubicin will effectively adhere to the nanoparticle and be released as the silicon degrades. Sailor has high hopes for the potential use of this novel nanotechnology. He summarizes, "the new design meets a growing need for nontoxic alternatives that have a chance to make it into the clinic to treat human patients".

Source: Park JH, Gu L, von Maltzahn G *et al.*: Biodegradable luminescent porous silicon nanoparticles for *in vivo* applications. *Nat. Mater.* DOI:10.1038/nmat2398 (2009) (Epub ahead of print).

Novel peptide identified that may broaden target population for stem cell vaccine

The biotechnology company, ImmunoCellular Therapeutics Ltd, has announced its identification of new peptides that may expand the target patient population for a cancer stem cell vaccine candidate, ICT-121. The detection of new peptides for use in the vaccine may help overcome the constraint of many cancer therapies – that their use is limited to patients with certain HLA types. Manish Singh, CEO of ImmunoCellular Therapeutics Ltd, stated, "this is an encouraging finding for us, as it could dramatically increase the number of patients who may be able to someday benefit from our cancer stem cell therapies". ImmunoCellular Therapeutics Ltd is a clinical-stage company, whose "off the shelf" stem cell vaccine candidate for multiple cancer indications is expected to enter clinical trials during 2009.

Source: ImmunoCellular Therapeutics, Ltd; www.imuc.com/press/Feb2409-Immunocellular-Theraputics-Identifies-Novel-Peptides-to-Broaden-Applicability-of-Cancer-Stem-Cell-Vaccine.html

Priority Paper Alerts

Wrap53, a natural p53 antisense transcript required for p53 induction upon DNA damage

Mahmoudi S, Henriksson S, Corcoran M *et al.*: *Molecular Cell* 33, 462–417 (2009).

This study identified *Wrap53* as the natural antisense transcript of *p53*, a gene well known for its link to cancer. *Wrap53* regulates endogenous *p53* mRNA levels, and siRNA knockdown of *Wrap53* resulted in decreased *p53* mRNA and suppression of *p53* induction upon DNA damage. Blocking of potential *Wrap53*/*p53* hybrids reduced *p53* levels almost as effectively as *Wrap53* knockdown, suggesting that *Wrap53* regulates *p53* through *Wrap53*/*p53* RNA interaction. The *p53* gene has previously been shown to protect against cancer, and this research implies that damage to *Wrap53* can indirectly cause carcinogenesis. This discovery not only reveals the regulatory pathway for a cancer-linked gene, but also proposes a general mechanism for antisense mediated gene regulation in humans.

***IDH1* and *IDH2* mutations in gliomas.**

Yan H, Parsons DW, Jin G *et al.*: *N. Engl. J. Med.* 360, 765–773 (2009).

This study identified mutations in two genes that have potential as therapeutic targets in malignant glioma. The sequence of the *IDH1* and *IDH2* genes was studied in 445 CNS tumors and 494 non-CNS tumors. The enzymatic activity of proteins produced from normal and mutant *IDH1* and *IDH2* genes was determined, and it was found that mutations that affected amino acid 132 of *IDH1* were present in more than 70% of WHO grade II and III astrocytomas, oligodendrogliomas, and in glioblastomas that developed from these lower-grade lesions. Tumors that did not possess mutations in *IDH1* often had mutations in the analogous amino acid of the *IDH2* gene. It was found that tumors with *IDH1* or *IDH2* mutations had specific genetic and clinical attributes. Further to this, patients with tumors that had *IDH1* and *IDH2* mutations had a better outcome than those with wild-type *IDH* genes.